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14. ABSTRACT

This second annual report reviews progress towards completing each of our three study tasks. Major accomplishments include IRB renewal for all study protocols, hiring and training of new staff at MGH, as well as the completing subject enrollment for Task 1 and continuing enrollment for Task 3. In study Task 1 we aim to determine the sex- and race-ethnicity-specific bone traits that may contribute to stress fracture risk in military recruits. We are ahead of schedule by increasing our study size and completing study enrollment, with 185 subjects enrolled (n= 50 White women, 50 White men, 51 Black women, 34 Black men). Data analysis and manuscript preparation are underway. In study Task 2 we aim to quantify changes in bone structure and bone metabolism in recruits before and after Basic Combat Training (BCT). Enrollment and data collection are complete, and data analysis is ongoing. Finally, for study Task 3 we aim to characterize recovery and predict bone-healing trajectories and develop return-to-duty guidelines. We hypothesize that changes in bone health during recovery from stress-fracture injury can be quantified and used to develop evidence-based RTD. Enrollment is underway, with 13 women with recent stress fracture enrolled.

15. SUBJECT TERMS
bone microarchitecture, HRpQCT, race, gender, sex, bone mineral density, vBMD, bone geometry, stress fracture

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Introduction:
Among the most common musculoskeletal injuries, lower extremity stress fractures remain a vexing problem for the military. Their occurrence leads to lost duty days and significant costs. This project involves three distinct studies aimed at improved understanding of pathophysiology of stress fractures and return to duty guidelines. The first (*Task 1*) is a cross sectional study aimed at identifying the bone properties that may be related to the well-known sex and race/ethnicity differences in risk for stress fracture. In this study, we will assess bone mineral density at the hip and spine, as well as bone microarchitecture at the distal tibia in young adult women (n=50 White and n=50 Black) and men (n=10 White and n=10 Black). We hypothesize Black individuals will have more favorable bone microstructure parameters than White individuals, and that men of both races will have more favorable bone microstructure parameters than women.

The second project (*Task 2*) is a longitudinal study that characterizes changes in bone structure and metabolism during Basic Combat Training (BCT). Specifically, the project team will measure serum markers of bone turnover and bone microarchitecture at the distal tibia in men and before and after Basic Combat Training (BTC). We hypothesize that subtle changes in bone health during BCT (which may lead to eventual stress fracture) can be characterized by changes in micro-scale structural and functional bone measures and by changes in biochemical bone markers.

Our third study arm (*Task 3*) is longitudinal and designed to measure bone microarchitecture and serum markers of bone metabolism in female athletes (n=30) throughout their recovery from stress fracture of the tibia. Our collaborators will use these data to perform analyses and develop mathematical models to predict bone healing trajectories and return-to-duty (RTD) guidelines. We aim to quantify how bone properties change during recovery from stress fracture, leading to the development of predictive models for bone healing following stress fracture and RTD guidelines. We hypothesize that changes in bone microarchitecture and metabolism during recovery from stress fracture injury can be quantified and used to develop quantitative RTD guidelines. We assume that recovery after injury follows the reverse process of stress-fracture development. That is, bone health measures after recovery tend to revert back to "normal," pre-injury values after complete healing.

Table 1. List of objectives from statement of work and current status

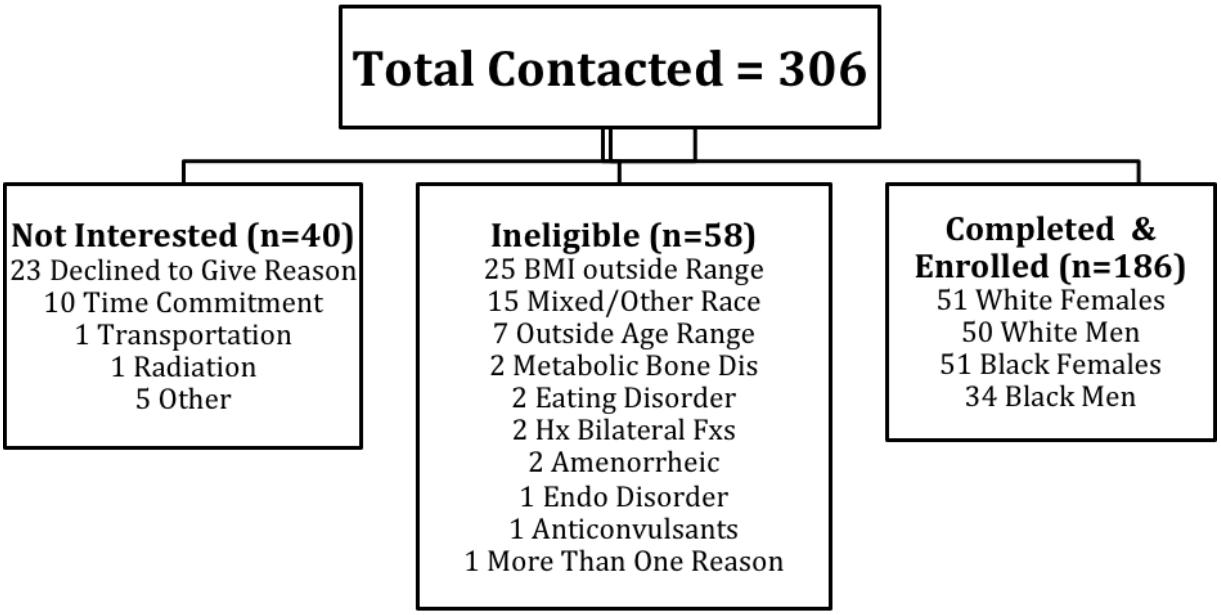
	Objectives from Statement of Work	**Status**
Task #1	1) Obtain Institutional Review Board (IRB) approval [month 1-6]	**Done**
	2) Renew IRB protocol [month 13-18, month 21-36]	**Pending**
	3) Acquire and analyze high-resolution peripheral quantitative computed tomography (HR-pQCT) images for 120 subjects [100 female (50 Caucasian and 50 African-American) and 20 male; [month 7-28]	**Done**
	4) Perform standard whole bone finite element analysis [month 7-28].	**Done**
	5) Perform data cleaning and statistical analyses [month 7-30]	**Ongoing**
Task #2	1) Assist with all aspects of study, including planning study logistics, collection of HR-pQCT data, analysis of HR-pQCT images, data analysis and interpretation	**Ongoing**
Task #3	1) Obtain IRB approval [month 4-9]	**Done**
	2) Renew IRB approval [month 16-21 and 28-33]	**Pending**
	3) Acquire and analyze HR-pQCT images and blood samples during stress-fracture recovery for 30 female subjects [month 10-36].	**Ongoing**
	4) Perform data cleaning and statistical analyses [month 10-36].	**Ongoing**

Body

Task 1: Characterize structural and functional differences in bone health that stratify high-risk (female; Caucasian) vs. low-risk (male; African-American) recruits [month 1-33]

Progress to date: We received Institutional Review Board (IRB) approval from Massachusetts General Hospital (MGH) in May 2015 and HRPO approval in August 2015 (task 1, objective 1). We renewed the IRB protocol in the spring of 2016, and will renew again in the spring of 2017 (task 1, objective 2). We aimed to complete enrollment by month 28. We have increased our enrollment target for men from 10 total to 85 total and are currently fully enrolled with 186 subjects, including 51 Caucasian women, 51 African-American women, 50 Caucasian men, and 34 African-American men (Figure 1)(task 1, objective 3). We have completed the data entry and image analysis on all 186 subjects (task 1, objectives 4 and 5). Scans have been sent to the PI and his BHSAI for further analysis.

Fig 1. Recruiting efforts and enrollment for Task 1.



Preliminary data analysis (task 1, objectives 3-5): We have completed data entry, cleaning, and preliminary statistical analysis for 186 subjects. We excluded one Caucasian woman due to a BMI that was beyond our inclusion range. For these subjects, basic demographics and selected bone parameters are presented in Table 2 and 3, respectively.

Table 2. Demographic characteristics of completed study subjects. Values are Mean (Standard Deviation)

	Caucasian Women n=50	Black Women n=51	Caucasian Men n=50	Black Men n=34
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (yrs)	24.5 (2.85)	22.2 (3.15)	24.9 (3.18)	24.3 (3.62)
Height (cm)	164.9(10.78)	166.1 (7.91)	179.9 (8.0)	177.8 (7.4)
Weight (kg)	63.4 (9.58)	64.4 (10.20)	78.5 (11.5)	78.2 (11.4)
BMI (kg/m$^{2)}$	23.3 (3.22)	23.3 (2.46)	24.2 (2.9)	24.9 (3.4)
Age of menarche (yrs)	12.8 (1.6)	11.8 (1.3)		
	n (%)	**n (%)**	**n (%)**	**n (%)**
Facture history	18 (36.0%)	4 (7.8%)	24 (480%)	6 (17.6%)
Highest education degree				
High School	0 (0%)	3 (6%)	0 (0%)	6 (17.6%)
Bachelors	44 (88%)	45 (88%)	39 (78%)	26 (75.4%)
Graduate	6 (12%)	3 (6%)	11 (22%)	2 (6%)
Family income				
Less than $20K	0 (0%)	6 (11.8%)	0 (0%)	4 (11.7%)
$20K to $99K	27 (54%)	27 (52.9%)	14 (28%)	22 (64.8%)
$100K or more	23 (46%)	18 (35.3%)	36 (72%)	8 (23.5%)
Contraceptive use				
Current use	37 (74%)	13 (25.5%)		
Past use	7 (14%)	9 (17.6%)		
Never Used	6 (12%)	29 (56.9%)		

Table 3. Selected results from high-resolution peripheral computed tomography (HRpQCT) scans at the tibia. Values are unadjusted Mean (SD)

	Caucasian Women n=50	African American Women n=51	Caucasian Men n=50	African American Men n=32	p race	p sex	P race/sex interaction
Size parameters							
Apparent Cortical Thickness (mm)	0.801 (0.16)	0.937 (0.19)	0.937 (0.17)	1.080 (0.23)	0.00	0.00	0.9
Cortical Perimeter (mm)	115.8 (8.05)	113.5 (8.49)	130.8 (10.43)	127.4 (9.73)	0.04	0.00	0.7
Cortical Area (mm^2)	90.6 (15.44)	103.5 (20.6)	120.6 (18.17)	135.5 (29.59)	0.00	0.00	0.8
% Cortical area (mm^2)	10.7 (2.30)	12.4 (11.58)	11.2 (2.44)	12.8 (2.73)	0.00	0.2	0.9
Trabecular Area (mm^2)	779.0 (114.9)	750.8 (127.3)	982.3 (168.99)	934.28 (146.71)	0.07	0.00	0.6
Total Area (mm^2)	864.9 (115.25)	850.1 (129.42)	1097.8 (168.19)	1064.9 (153.55)	0.27	0.00	0.7
Microarchitecture parameters							
Cortical Porosity (%)	4.29 (1.46)	3.22 (1.07)	6.05 (2.13)	4.81 (2.06)	0.00	0.00	0.7
Trabecular Number (1/mm)	2.18 (0.26)	2.14 (0.28)	2.35 (0.29)	2.18 (0.32)	0.02	0.02	0.2
Trabecular Thickness (mm)	0.076 (0.01)	0.083 (0.010)	0.081 (0.01)	0.089 (0.01)	0.00	0.00	0.7
Trabecular Separation (mm)	0.388 (0.05)	0.392 (0.06)	0.351 (0.06)	0.380 (0.07)	0.08	0.01	0.2
Heterogeneity of Network (mm)	0.161 (0.03)	0.168 (0.03)	0.146 (0.04)	0.165 (0.04)	0.02	0.06	0.3
Density Parameters							
Cortical Bone Mineral Density (mmHA/cm^3)	872.9 (38.20)	908.37 (35.33)	846.5 (42.24)	891.4 (36.06)	0.00	0.00	0.4
Cortical Tissue Mineral Density(mgHA/cm^3)	930.0 (30.59)	950.2 (29.25)	920.8 (27.29)	950.3 (25.82)	0.00	0.3	0.3
Trabecular Bone Density (mgHA/cm^3)	197.8 (31.43)	213.2 (35.34)	229.0 (41.37)	233.3 (39.71)	0.08	0.00	0.3
Total Bone Density (mgHA/cm^3)	262.6 (40.07)	292.7 (46.42)	292.8 (51.23)	314.20 (52.43)	0.00	0.2	0.5
μFEA-Estimated Strength Parameters							
Stiffness (kN/mm)	211.58 (38.50)	245.71 (52.95)	304.28 (52.81)	333.14 (69.79)	0.00	0.00	0.7
Failure Load (KN)	10.84 (1.86)	12.43 (2.62)	15.50 (2.54)	16.71 (3.45)	0.00	0.00	0.6

Task 2: Quantify changes in bone health before and after basic combat training (BCT) [month 1-33]

Progress to date: We assisted our colleagues at USARIEM in the successful enrollment and data collection for Task 2. The study was conducted at Fort Jackson, with 174 subjects completing baseline assessments and 161 subjects (65 White women, 49 Black women, 35 White men, 12 Black men) completing both the baseline and follow-up assessments.

We are currently assisting in ongoing efforts to complete the image analysis, data analysis and interpretation. For 99 women subjects, basic demographics and selected bone parameters are presented in Table 4 and 5, respectively.

Table 4. Demographic characteristics of completed study subjects. Values are Mean (Standard Deviation)

	Baseline Mean (SD)	**Follow-up Mean (SD)**	**p**
n	99	91	
Age (yrs)	21.5 (3.29)		
Height (cm)	162.2 (7.087)		
Weight (kg)	62.4 (9.55)	63.2 (8.62)	NS
BMI (kg/m^2)	23.7 (2.82)	23.9 (2.36)	NS
Body Fat (%)	23.9 (4.32)	21.4 (3.56)	<.001

Table 5: Change in bone microarchitectural measurements from baseline to end of BCT.

	Unadjusted		Adjusted*	
Variable	**% Change** (95% CI)	**P-Value**	**% Change** (95% CI)	**P-Value**
Total vBMD	1.77 (1.30, 2.25)	<0.0001	1.79 (1.32, 2.25)	<0.0001
Trabecular vBMD	2.00 (1.43, 2.56)	<0.0001	2.01 (1.44, 2.58)	<0.0001
Trabecular #	1.21 (0.49, 1.93)	0.0013	1.21 (0.48, 1.94)	0.0013
Trabecular Thickness	1.13 (0.76, 1.51)	<0.0001	1.13 (0.76, 1.50)	<0.0001
Trabecular Spacing	-1.08 (-1.61, -0.56)	<0.0001	-1.09 (-1.61, -0.56)	<0.0001
Trabecular BV/TV	1.85 (1.29, 2.41)	<0.0001	1.87 (1.31, 2.43)	<0.0001
Cortical vBMD	-0.35 (-0.56, -0.14)	0.0012	-0.34 (-0.55, -0.14)	0.0014
Cortical Thickness	0.98 (0.37, 1.59)	0.0018	0.98 (0.38, 1.58)	0.0016

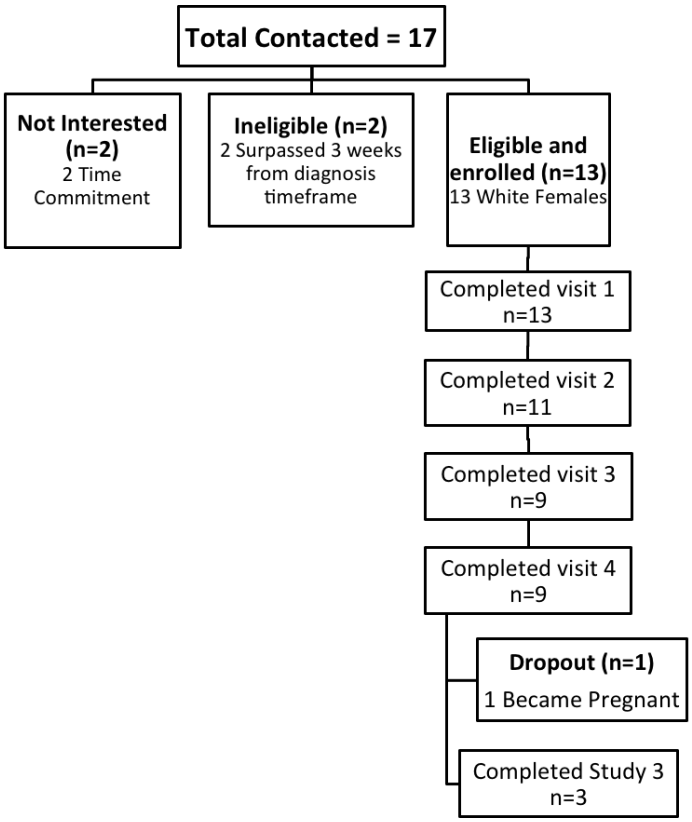
* Model adjusted for race/ethnicity, age, and BMI

Task 3: Characterize injury recovery and develop a model for predicting bone-healing trajectories and return to duty (RTD) [month 1-33]

Progress to date: We obtained IRB approval for the study from MGH in May 2015 and HRPO approval for the study in August 2015 (Task 3, objective 1). We received IRB renewal in the Spring of 2016 and will apply again in the Spring of 2017 (Task 3, objective 2). We have enrolled 13 subjects to date with 1 dropout. We lost 2 eligible subjects due to the closure of our bone density center after a fire. As of 10/31/16 the bone density center is operational and we have resumed enrollment. We have increased enrollment efforts and are collaborating with local sports medicine physicians, coaches, and athletic trainers to continue recruiting effectively. Additionally, we have developed a newsletter to foster support from the local athletic community and gained permission to search physician and radiology notes through the MGH Research Patient Data Registry (RPDR) (Task 3, objective 3). HR-pQCT and DXA images are being analyzed and entered as they

are acquired. We are freezing and storing blood samples and plan to send these in batches to USARIEM for analysis (Task 3, objective 4).

Fig 2. Recruiting efforts and study visit progress for Task 3.



Key Research Accomplishments:

- Obtained IRB renewal from MGH for Task 1 and Task 3
- Recruited, hired, and trained new MGH study staff
- Completed enrollment for Task 1
  - Target recruitment was 30 subjects by 3/1/16 and 60 by 8/1/16
  - As of 10/1/16 we were fully enrolled.
- Completed data collection for Task 1
- Completed data entry and cleaning for Task 1
- Started data analysis for Task 1
- Continued recruitment and enrollment for Task 3
- Started data entry, cleaning, and analysis for Task 3
- Hired and trained additional study staff to assist with recruiting, data collection, and data cleaning
- Held and continue to hold bi-monthly study team meetings with USARIEM and BHSAI

Reportable Outcomes:
Not Applicable, as data collection is currently ongoing.

Conclusion:
This research is important to determine factors that predispose individuals to stress fracture as well as predict return-to-duty for those who have incurred a stress fracture. Enrollment and data entry have been completed for Task 1. Analysis and manuscript preparation are in progress. Task 2 enrollment and data entry are complete. Analysis is in progress. Recruitment and data entry are in progress for Task 3. While we are ahead of the projected timeline regarding our statement of work for Task 1, we are behind in recruitment for Task 3. We have recently increased our recruiting efforts by establishing new relationships within the medical and athletic community. We anticipate this effort will require great persistence and communication to reach our enrollment goal.

Personnel receiving pay:
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